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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	PAPER NUMBER
1648	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,325	BIRKETT, ASHLEY J.	
	Examin r	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cov r sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) *12,18,21,31,38,44,47,50,52,55,59,66 and 68-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 13-17, 19, 20, 22-30, 32-37, 39-43, 45, 46, 48, 49, 51, 53, 54, 56-58, 60, and 67* is/are rejected.

7)☒ Claim(s) *61-66* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-75 are pending in the present application. Claims 12, 18, 21, 31, 38, 44, 47, 50, 52, 55, 59, 66, and 68-75 are withdrawn as to non-elected inventions, and claims 1-11, 13-17, 19, 20, 22-30, 32-37, 39-43, 45, 46, 48, 49, 51, 53, 54, 56-58, 60-65, and 67 are under consideration to the extent that they read on the elected embodiment.

Election/Restrictions

2. Applicant's election without traverse of Group I, and Subgroup A, and the species wherein the B-cell epitope comprises SEQ ID NO: 3, and the T-cell epitope is EYLNKIQNSLSTEWSPC SVT, in Paper No. 12 is acknowledged.

3. Claims 68-75 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12.

Specification

4. The disclosure is objected to because of the following informalities: on page 10, the first full paragraph, the application introduces HBcAg by use of this acronym, which is further identified as HBc. However, in this introduction, the application does not first identify the

protein being discussed by its full name along with the acronym used through the specification. It is requested that the full name of the protein be inserted where the protein is introduced.

Also, while it is assumed that the application intended to identify HBc as an abbreviation for HBcAg, the application instead refers to HBc as an abbreviation for HbcAg.

Appropriate correction is required.

Claim Objections

5. Claims 61-66 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must depend from multiple claims in alternative form only. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 9-11, 13-17, 19, 20, 22-26, 35-37, 39-43, 45, 46, 48, 49, 51, 53, 54, and 56-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims describe a recombinant HBc protein wherein Domain III of the protein "consists essentially of the HBc sequence from position 86 through position 135" and Domain IV of the protein is peptide bonded to the residue at potion 135, and Domain II comprises residues 76 to 85 of HBc. This claim is indefinite because it is not clear what is meant by the requirement that

Domain III "consists essentially of the HBc sequence from position 86 through position 135." This indefiniteness arises, in part, from the requirements of the claim that Domain III is surrounded on one side by a sequence terminating with residue 85 and on the other side by one that requires that it is bound to Domain III through a peptide bond with residue 135, and in part from the use of the language "consisting essentially of."

Consisting essentially of implies that there are other residues that may be inserted at either end of the disclosed range of amino residues that would not affect the described peptide. However, it is unclear what other residues may be included as the residue positions included in Domain III as the HBc residues that Domain III may comprise have been boxed in by the surrounding Domains. Since residues 85 and below would be part of Domains I or II, and residues 136 and above are of Domain IV, there are no other residues of which Domain III could comprise. Therefore, it is unclear what is meant by the "consists essentially of" in the context of range of the residues included in Domain III.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-5, 7, 8, 27-30, 32-34, 60, and 67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for chimeric HBc molecules wherein HBc residues 1-4 have been replaced, does not reasonably provide enablement for HBc chimers

where these residues are absent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The claims read on a recombinant HBc protein including "at least the sequences of the residues of position 5 through position 75 of HBc." However, on pages 29-30 of the specification, the application states that HBc chimers that contains deletions of more than the first three N-terminal amino acids results in complete disappearance of the molecules in E. coli, where no other sequence is substituted into those positions. As the application seems to indicate that HBc proteins cannot exist without the residues prior to position 5, the application is not enabled for HBc chimers that have "at least" the residues after position 5.

10. Claims 9-11, 13-17, 19, 20, 22-26, 35-37, 39-43, 45, 46, 48, 49, 51, 53, 54, and 56-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims refer to an embodiment of the claimed chimeric HBc where Domain III of the protein "consists essentially of" residues 86-135 of the HBc protein. This claim is rejected for lack of written description because the specification provides no descriptive support indicating what sequences or residues other than residues 86-135 may be included in the sequence of this Domain. See e.g., App. pages 29 and 32, each indicating that Domain III of the chimeric protein is limited to the identified range of amino residues. As no other descriptive support is provided indicating the Domain III may comprise residues other than those of HBC

residues 86-135, there is inadequate written description support for the language "consists essentially of" with reference to the constitution of Domain III.

11. Claims 1-11, 13-16, 19, 22-24, 26-30, 32-37, 39-42, 45, 48, 49, 53, 54, 56-58, 60, and 67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for HBc chimeric proteins comprising insertions of the disclosed Plasmodium falciparum epitopes, does not reasonably provide enablement for an HBc chimeric protein wherein any Plasmodium epitope has been inserted in the protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification provides lists of closely related epitopes for four species of Plasmodium. Pages 31-32. The application discloses numerous other epitopes of several pathogens, including one Plasmodium epitope, which "failed to express when inserted" into the claimed HBc chimer. Pages 100-102. The application states that the reason for the failure of these epitopes to be expressed is unknown. Page 100. Because the applicant has shown that there are non-working Plasmodium epitopes, and because the applicant has not provided any guidance that one practicing the invention may use to determine what epitopes may and may not be expressed, the applicant is not enabled for HBc chimers comprising any Plasmodium epitope.

12. Claims 1-11, 27-30, 32-34, 56-58, 60 and 67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for HBc chimers wherein Domain IV of the protein comprises the HBc sequence of residues 136-140, does not reasonably provide

enablement for HBc chimers that do not comprise these residues in Domain IV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The claims read on HBc chimers wherein Domain IV of the protein comprises either the HBc residues 136-140, or at least 5 heterologous residues to substitute for these residues. However, although this is what the application describes in the specification (see page 32-33), the applicant has not shown that such embodiments of the claimed invention are operative.

On page 32 of the specification, the applicant states, "when the chimeric protein ends at HBc residue 135, desired, particularly immunogenic particles do not form. While it is not clear what is meant by this statement, it appears that the applicant is stating that where the protein lacks these residues it is not immunogenic. In view of the teaching of the art surrounding the importance of these residues, the applicant seems to be equating the immunogenicity of the chimer with the ability of the protein to self assemble. See, Metzger, J. Gen. Virol. 79:587-90 (teaching that HBc proteins are not able to self assemble without 1) at least one residue beyond residue 139, and 2) without a proline at position 138 of the protein). Such a relationship between self-assembly and immunogenicity likewise has support in the art. See, Kratz, PNAS 96:1915-1920, at 1918 (right column- stating "Assembly competence and surface exposure are hence essential to provoke a strong response against" an inserted epitope).

Immediately after the applications statement regarding the lack of immunogenicity of protein ending at residue 135, the application continues with a statement that the particles do form when Domain IV comprises either HBc residues 136-140, or 5 heterologous residues. The applicant and art support the operability of the proteins with residues 136-140. But, there is no

such evidence with regards to the operability of embodiments with only the at least 5 heterologous residues. See, pages 79-102 (providing working examples of the claimed protein wherein the HBc portion of the chimer appears to terminate at residue 149). Furthermore, the art surrounding the invention appears to indicate that such embodiments are not operative.

An example of such art is found in Metzger. This reference indicates that HBc proteins lacking amino residues after position 139, or wherein residue 138 is not a proline, are not able to self-assemble. Thus, the reference agrees with the applicant that a protein containing residues 136-140 would be operative. However, due to the requirement of a proline at position 138, it would appear from the reference that not every heterologous sequence substituted for residues 136-140 would result in an operative (self-assembling) protein. From the reference, it would appear that only those proteins with a proline at the position corresponding to residue 138 would result in an operative protein. Thus, the application is not enabled for proteins wherein any 5 heterologous residues are substituted for HBc residues 136-140. Further, an amendment requiring a proline at position 138 would not be supported by the application as filed.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-4, 6, 7-11, 13-17, 19, 20, 22-30, 32-37, 39-43, 45, 46, 48, 49, 51, 53, 54, 56-58, 60 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens

(Intervirology 38:63-74) in view of Nardin PCT (WO 98/31382), Nardin (Science 246:1603-1606), Schödel (J. Exp. Med. 180:1037-1046), Bernardi (DE 3741183), Kratz (PNAS 96 :1915-1920), and Metzger (J. Gen. Virol., 79 :587-590). The rejected claims read on recombinant HBc chimeric proteins comprising a Plasmodium falciparum B-cell epitope (B epitope) between HBc residues 78 and 79, and optionally including a T-cell Plasmodium falciparum epitope (T epitope) at the C-terminus of the protein.

Pumpens teaches the use of HBc as an epitope carrier for vaccines against non-hepatitis B pathogens. The reference teaches that epitopes may be added to the C-terminal and internal portions of the protein. Page 69, right column. According to Pumpens, among the best sites for insertion of the foreign epitopes is the surface region of residues 70-80 of the HBc protein. Page 66, left column. See also, Kratz, page 1915 (indicating that the HBc particle appears to have strong antigenic responses around amino acid 80, thereby indicating this region as a target for non-HBc epitope insertions.) The reference further identifies the region of residues 78-83 as a protein surface region into which B epitopes may be inserted. Page 70, left column. Thus, the reference renders it obvious to those in the art to make substitutions of foreign epitopes in the region of HBc residues 78-83. As the applicant has not identified any particular reason for choosing the insertion site of between residues 78 and 79, Pumpens has rendered this placement of the B epitope obvious.

Pumpens further teaches that, for C-terminal insertions, residues 144, 149, and 156 are preferred. However, the present claims also read on embodiments wherein the heterologous residues are added to residue 140 of the HBc protein. Pumpens indicates that residues 139-144 contain the residues required for self-assembly of the protein. Page 66. In view of the later

teachings by Metzger, one of ordinary skill in the art would have been lead to believe that C-terminal insertions could be made prior to residue 144, as residue 140 appears to be the minimum residue required for self-assembly.

The Pumpens reference does not teach or suggest making a chimer using Plasmodium epitopes, and thus does not alone render obvious the presently claimed chimer that uses specific epitopes and a combination of B and T cell epitopes. However, a motivation for using the Pumpens HBc chimer as a base for anti-malarial vaccines may be found in the teachings of Nardin (teaching an immunogenic peptide construct comprising a B and T cell Plasmodium epitope), and more directly, by Schödel (teaching an anti-malarial HBC protein with Plasmodium epitopes). Thus, from the art, one of ordinary skill in the art would have had both motivation to make an HBc protein comprisng Plasmodium falciparum immunogenic epitopes, and a reasonable expectation of success in doing so.

Once one of ordinary skill in the art had a motivation to make an anti-malarial HBc, it would likewise be obvious to such a person to use the B and T cell epitopes described by the claims. See e.g. Nardin, and Bernardi, teaching immunogenic Plasmodium B cell eptiopes according to the claims, and Nardin PCT disclosing the Plasmodium T cell epitope disclosed in the present application as SEQ ID NO: 148. As the epitopes of the present invention were known in the art, and as the art teaches that such epitopes may be inserted into the HBc chimer, it would have been obvious to use these epitopes in making an anti-malarial HBc chimeric protein.

Examiner's Notes

15. This note is in reference to claims 1-60 and 67 of the present application. These claims describe a recombinant hepatitis B virus core protein comprising four domains, the first domain (Domain I) of which is described as either comprising at least the sequence of residues 5-75, or consisting essentially of these residues, and the second domain (Domain II) which is described as "peptide-bonded to residue 75." The purpose of this note is to specify how these phrases are being interpreted for the prosecution of the claims. In most situations, the phrase "at least the sequence of the residues of position 5 through position 75" would normally be interpreted so as to allow other residues to either side of the disclosed sequence. However, in view of the fact that Domain II must be peptide-bonded to residue 75 Domain I, the claims are being interpreted such any additional residues in addition to those of 5-75 must be added to the N-terminal of this sequence. I.e., additional residues may be added prior to the residue of position 5, but not after the residue of position 75.

Conclusion

16. Claim 6 is objected to as dependant on a rejected claim.

17. No claims are allowed.

18. The following prior art references are made of record and are considered pertinent to applicant's disclosure. Although these references have been used in the rejections above, the relevance of each of these references is here summarized.

> DE 3741183, naming Bernardi et al. as inventors. Claim 1 of this reference discloses a peptide that comprises the B-cell epitope of SEQ ID NO: 3 in the present application. In view of the teachings by WO 98/31382 (page 2, lines 5-12), one in the art would have known this to be a B-cell Plasmodium epitope.

WO 98/31382, naming Nardin et al. as inventors. This publication discloses the use of an immunogenic protein comprising both a universal malaria T-cell epitope derived from P. falciparum, and a B-cell epitope. An example of such an epitope is disclosed as the $(NANP)_3$ peptide from the Plasmodium CS protein. Page 2, lines 5-12. One of the disclosed T-cell epitopes varies from the claims T-cell epitope in that the amino residues preceding the EYLNKIQNSLSTEWSPCSVT peptide are not taught by the reference. Page 2-3.

Kratz et al., PNAS 96 :1915-1920. This article teaches the use of the HBc protein as a carrier for non-hepatitis B antigens by inserting the foreign epitopes into the c epitope (around residue 80) of the HBc protein. Abstract, and page 1915. The reference teaches that such epitopes may be added to either the c epitope, or to the C terminus. Further, the reference teaches that it is preferable for the added epitopes not to affect the ability of the HBc particle to self assemble. The reference teaches that a complete protein may be inserted into the c epitope of HBc. However, it also states that insert sizes into the protein seemed to be limited to 50 amino acids. Page 1915. This teaching is still relevant to the present invention despite the teachings of the reference regarding the insertion of a complete 250 aa protein due to the reference's teaching that the ability of HBc to accept the larger sequence was due to two factors. Page 1919. First, the separation of the HBc into two stable elements (achieved by inserting the epitope into the HBc c epitope). Second, the reference also indicated that it is important that the inserted sequence be able to form a stable structure independently. This is relevant in due to the lack of teachings of such stability in the Plasmodium CS epitopes, thus indicating that the CS epitopes may be limited to 50 aa inserts. Kratz also teaches the use of unrelated peptide residues as linkers on either side of an inserted epitope. Page 1917, left column.

Metzger et al., J. Gen. Virol., 79 :587-590. This article teaches that at least the first 139 residues of HBc are required for any protein assembly, and that the protein assembly capability is maintained if residues 140-144 are present, and is fully maintained when residue 145 is present. This indicates that ideal HBc antigenic proteins (as these are taught to be self-assembling by Kratz) would have the C-terminal residues up to at least position 145.

Nardin et al., Science 246: 1603-1606. This article teaches that an effective malarial vaccine requires T-cell epitopes in addition to the B-cell epitopes already known when the reference was published. Pages 1603-1604.

Schödel et al., J. Exp. Med. 180:1037-1046. This reference teaches a chimeric HBc protein expressing Plasmodium antigenic eptiopes and raising anti-malarial antibodies. However, the reference does not teach the currently claimed HBc chimeric protien, or suggest the speicifc insertion sites used in the presently claimed invention.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
February 5, 2003

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